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14. ABSTRACT <b>A recent manuscript [1] described two multi-center, prospective double blind trials of the non-absorbed antibiotic rifaximin for nonconstipated irritable bowel syndrome (IBS). This effort adds to the body of literature from other, smaller studies that have demonstrated clinical efficacy for IBS with rifaximin. Non-absorbed antibiotics have been endorsed by the American College of Gastroenterology IBS Task Force as potentially useful therapy for IBS [2]. Interest in this approach stems from the increasing recognition of enteric bacterial imbalances in some patients with IBS compared to non-IBS controls [3-4]. An early study of antibiotics for IBS involved 87 patients with IBS randomized to rifaximin 400 mg three times daily for 10 days or placebo. During the initial 2 weeks of therapy and the subsequent 10 weeks of follow-up rifaximin resulted in statistically significantly greater improvement in IBS symptoms than placebo [5]. The report by Pimentel et al. represents a significant advance in our knowledge and understanding of the effects of rifaximin for IBS.</b>					
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## Non-absorbed Antibiotics for IBS

Brooks D. Cash\*

Professor of Medicine, USUHS, Chief of Medicine, NNMC, Gastroenterology, Bethesda, USA

A recent manuscript [1] described two multi-center, prospective, double blind trials of the non-absorbed antibiotic rifaximin for non-constipated irritable bowel syndrome (IBS). This effort adds to the body of literature from other, smaller studies that have demonstrated clinical efficacy for IBS with rifaximin. Non-absorbed antibiotics have been endorsed by the American College of Gastroenterology IBS Task Force as potentially useful therapy for IBS [2]. Interest in this approach stems from the increasing recognition of enteric bacterial imbalances in some patients with IBS compared to non-IBS controls [3-4]. An early study of antibiotics for IBS involved 87 patients with IBS randomized to rifaximin 400 mg three times daily for 10 days or placebo. During the initial 2 weeks of therapy and the subsequent 10 weeks of follow-up, rifaximin resulted in statistically significantly greater improvement in IBS symptoms than placebo [5]. The report by Pimentel et al. represents a significant advance in our knowledge and understanding of the effects of rifaximin for IBS.

Clinical trials evaluating therapies for IBS are difficult to conduct and the results must be interpreted carefully. While IBS is a common condition, it is also a very subjective one, with no identified or reliable biomarkers. Thus, the diagnosis of IBS is made after careful exclusion of other pathophysiological disturbances that could result in the hallmark symptoms of abdominal pain accompanying altered bowel habits and application of symptom-based criteria such as the Rome diagnostic criteria for IBS [6-8]. Therein lays one of the difficulties in IBS research. The Rome criteria continue to evolve based on updated and accumulated research surrounding the pathophysiology and diagnostic approaches to IBS. The difficulty in adhering to a single diagnostic criterion, over time, among studies of IBS therapies limits the conclusions that can be drawn from the results of these studies when considered in the larger context of the IBS therapeutic milieu. Because IBS is a subjective condition, the severity from patient to patient is widely variable. Establishing reliable and reproducible barometers for determining severity of IBS symptoms and their impact are sorely needed as inclusion of patients with differing degrees of severity could affect the results of clinical trials of therapeutic agents and lead to the promotion of misleading conclusions that may not translate to clinical practice. Severity of patients in clinical trials is also paramount to consider when transferring the therapeutic approaches from trials into routine clinical practice. Additionally, the clinical endpoints of IBS therapeutic trials can be a difficult maze to negotiate. Some trials have evaluated the effects of therapy on individual IBS symptoms while others use a composite IBS score or global response as their measure of efficacy. Still others use physiologic, rather than clinical, endpoints. Over the last decade, the Food and Drug Administration has favored a global IBS endpoint for Phase 3 clinical trials conducted with the goal of achieving drug approval for an indication for IBS. It remains unclear if this is the optimal approach, especially since so much of the routine clinical practice surrounding IBS is directed at alleviating the individual symptoms that patients manifest, and in so doing hopefully improving the "global response". Finally, issues such as the way symptoms are elicited, the number of return visits during a clinical trial and whom those visits are with, can all bias the results of therapeutic trials for IBS.

In the current analysis, the methodology used by the investigators was straightforward and superb. Both of the studies were large (n=623

for TARGET 1; n=637 for TARGET 2) and conducted in multiple sites throughout the US and Canada in patients with mild to moderate symptoms of non-constipation IBS according to the Rome II IBS diagnostic criteria [7]. After a 1-2 week screening phase to confirm that patients fulfilled the eligibility requirements, patients were randomly assigned via concealed allocation to either rifaximin or placebo, in a 1:1 ratio. After completing the 14-day treatment period, patients were evaluated for 10 additional weeks, in order to monitor the short-term durability of treatment effects and symptoms. It should be noted that by convention most high-quality IBS therapeutic trials are at least 12 weeks in duration, due in part to recommendations by the Rome Committee and the FDA. Efficacy assessments were obtained daily by means of an interactive voice-response system over the course of the entire study and a clearly defined endpoint, adequate relief of global IBS symptoms for at least 2 of the 4 weeks during the primary evaluation period based on a binary response to a Yes/No question. A key secondary endpoint, satisfactory relief of bloating, was assessed in similar fashion as the primary endpoint over the same period of time.

In both studies, patients consistently fulfilled the criteria for relief of global IBS symptoms and bloating. A statistically significant proportion of patients randomized to the rifaximin group, compared to those that received placebo, had adequate relief of global IBS symptoms (41% vs. 32% pooled data,  $P<0.001$ ) and bloating (40% vs. 30% pooled data,  $P<0.001$ ) for at least 2 of the first 4 weeks of the treatment assessment period. Moreover, these results were durable, with statistically significant differences favoring rifaximin for the relief of global symptoms and bloating through the 10 week post treatment observation period. Other important individual symptoms of IBS were assessed, including abdominal pain and stool consistency and these endpoints were also more likely to improve with rifaximin compared to placebo. As with any clinical trial involving a therapy, safety was evaluated and no clinically significant differences were observed in terms of treatment emergent adverse events between patients randomized to either treatment arm.

The top-line results of these two studies appear quite favorable, and reinforce what many clinicians have been doing with rifaximin for several years, in an off-label fashion. Clinical experience has demonstrated that rifaximin can significantly improve the gastrointestinal symptoms of some IBS patients. These results, from two large and well-designed clinical trials offer convincing evidence that the results observed anecdotally for the last several years are in fact consistent and reproducible. The differences observed for the primary and secondary

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**\*Corresponding author:** Brooks D. Cash, MD, FAGC, AGAF, Professor of Medicine, USUHS, Chief of Medicine, NNMC, 8901 Wisconsin Avenue, Bldg 9, Gastroenterology, Bethesda, MD 20889, USA, Tel: 301-295-4585; Fax: 301-295-4599; E-mail: [brooks.cash@med.navy.mil](mailto:brooks.cash@med.navy.mil)

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endpoints between rifaximin and placebo, while only 9%-10% were similar to treatment differences observed in other phase 3 clinical trials of medications that received FDA approval as therapies for IBS such as alosetron, tegaserod, and lubiprostone [9-11]. The promising results of TARGET 1 and TARGET 2, however, do not completely clear up the issues surrounding the use of rifaximin for IBS. One of the most important questions remaining is the optimal means by which rifaximin responders can be identified. Some have suggested that breath test evidence of small intestinal bacterial overgrowth (SIBO) be used as treatment criteria but the previous, smaller studies of rifaximin have not convincingly demonstrated that positive breath testing correlates well to clinical response to rifaximin and breath testing for SIBO can be difficult to obtain and perform [5]. As a practical matter, many clinicians have used positive breath tests to obtain third party reimbursement for rifaximin, which is an expensive medication in the 1200-1650 mg doses used for IBS, another issue complicating this approach. Another question surrounding the use of antibiotics such as rifaximin, as well as agents such as probiotics, as IBS therapies is exactly how they are exerting an effect on the gastrointestinal tract of patients with IBS who respond to these therapies. Popular theories hold that these medications, antibiotics especially, decrease the density of fermenting bacteria in the small bowel, but there are other theories, such as anti-inflammatory effects that lead to alterations in enteric motility, secretion and sensitivity that have been put forth as possible explanations. Another concern surrounds the possibility of resistance, but there is abundant data in the literature demonstrating the safety of rifaximin with respect to this issue that should assuage clinicians and regulatory authorities, alike [12].

Finally, one of the most pressing questions, and one that was raised by the FDA in their review of this data during the approval deliberations for rifaximin, is the durability of response. While treatment differences between rifaximin and placebo did persist throughout the conclusion of 12-week study period, a gradual diminution of the relief of global IBS symptoms and bloating was observed in both groups as the trial progressed. This observation also mirrors the community-based clinical experience observed with rifaximin. While there can be a dramatic response in some patients, symptom recurrence at a variable point after rifaximin treatment has concluded appears common. While the FDA did not specifically ask to look at recurrence and retreatment data a priori, the issue led to a Complete Response Letter to be issued by the FDA based on their deliberations of this data, rather than an Indication Approval. This is unfortunate because neither TARGET 1 nor TARGET 2 were designed to address this issue and it is likely that additional studies will need to be performed before this issue can be fully addressed. It is also a curious response, given the fact that that other agents that are used for short term relief of IBS have not typically been subjected to this level of scrutiny regarding retreatment and the body of evidence surrounding the safety of rifaximin for short term use in traveler's diarrhea and long-term use in hepatic encephalopathy is excellent. Nevertheless, recurrence and retreatment effects with rifaximin, or any other antibiotic being used for IBS, are crucial to obtain as there is very little guidance in the literature. What data that do exist suggests that rifaximin responders who experience recurrent IBS symptoms will respond with retreatment [13]. Should patients who respond to rifaximin be treated with a two week course of therapy every 4-6 months, what are the effects and safety of daily therapy perhaps at lower doses or shorter duration "rescue" regimens, can other agents be used to increase or prolong the therapeutic response to rifaximin, and what are the cost implications of all of these approaches, compared with alternative therapeutic approaches to non-constipated IBS patients? The report by Pimentel and colleagues is an important piece of additional evidence that IBS can be effectively treated and managed

and sheds light on the clinical effects of this treatment for this common and costly condition. However, the report also raises additional questions that will require additional study and time to answer.

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